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Narrative review

Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans

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ABSTRACT

Background: Cytology-based screening has been a cornerstone of cervical cancer prevention for decades. Following extensive evidence demonstrating higher sensitivity and accuracy, lower variability and better reproducibility of human papillomavirus (HPV)-based screening compared with conventional or liquid-based cytology, recent European guidelines strongly recommend primary HPV-based screening over standard cytology-based screening. In addition, HPV-based screening offers the possibility of self-sampling and makes possible longer screening intervals in women with negative screening results.

Objectives: We summarize the current status of implementation of HPV-based screening in Europe, describe the real-life experience and challenges from countries already performing HPV-based screening, and briefly review immediate and long-term plans for screening implementation in selected European countries.

Sources: Data were obtained from peer-reviewed literature, personal communication with experts and authorities involved in formulating national recommendations and practical guidelines, and relevant national websites.

Content: As of July 2019, the Netherlands and Turkey are the only European countries with fully implemented national HPV-based cervical cancer screening. Italy, Sweden and Finland have already implemented HPV-based screening in several regions, and several other countries are at various stages of implementation. Some countries are considering transitioning from cytology-based to HPV-based screening, but are struggling with the suboptimal performance of current population-based programmes. Implementation of HPV-based screening has resulted in higher colposcopy referral rates, but also higher detection rates of CIN3+ lesions and cervical cancers requiring immediate treatment. Cytology is mostly used as a triage test, although other strategies are under consideration in some countries.

Implications: HPV-based screening is best suited in organized population-based screening settings. In 2019, cervical cancer screening policies across Europe vary greatly. Experience in countries with national and regional HPV-based screening already implemented is generally very positive. Urgent action is needed in many European countries, especially those with suboptimal opportunistic cytology-based cervical cancer screening. **P.J. Maver, Clin Microbiol Infect 2020;26:579**

Introduction

In 2018, the World Health Organization (WHO) called for coordinated global action to eliminate cervical cancer, ensuring that all girls are vaccinated against human papillomaviruses (HPVs) and that every woman over 30 years is screened and treated for precancerous lesions [1]. A recent modelling study showed that widespread coverage of both HPV vaccination and cervical cancer screening from 2020 onwards could prevent 12.5–13.4 million new cases of cervical cancer by 2070 and could achieve near-elimination of cervical cancer in most countries by the end of the century [2]. It should be emphasized that primary prevention (HPV vaccination) and secondary prevention (cervical cancer screening) are equally important components of elimination strategies because they act

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additively by intervening at different points in the natural history of cervical cancer and imply actions in women of different ages [3].

How and when to use primary HPV-based screening

Cytology-based screening has been a cornerstone of cervical cancer prevention for decades. However, it requires maintenance of complex infrastructure and highly trained personnel, and relatively short screening intervals are necessary for maintaining accuracy. Although the specificity of cytology is generally very high, sensitivity for detecting cervical intra-epithelial lesions grade 2 or more (CIN2+) is substantially lower than HPV testing and varies considerably between studies, ranging from 18.6% to 76.7% [4]. Following extensive evidence that HPV-based screening provides far greater and longer protection against invasive carcinomas than cytology-based screening [5–8], supplements to the European guidelines for quality assurance in cervical cancer screening were developed and published in 2015, including 36 graded recommendations dealing with various aspects of HPV-based screening [9,10].

Due to lower specificity, HPV-based screening should not be used in women under 30 and in some settings under 35 [9,10]. In addition, an HPV-positive screening result requires appropriate triage, referral, and repeat testing with a clear algorithm established within a cervical cancer screening programme [9,10]. In most countries, cytology is used as a triage test following a positive HPV screening result, avoiding direct referral to colposcopy; further management depends on the cytology result (referral to colposcopy or repeat testing).

An HPV-negative screening result allows safe extension of the screening interval, which was clearly demonstrated in a 14-year follow-up of a population-based randomized cohort in the Netherlands, where the cumulative incidence of cervical cancer and CIN3+ among HPV-negative women after three screening rounds at 5-year intervals was similar to the corresponding cumulative incidence among cytology-negative women after two screening rounds [11]. Therefore, the recommended screening interval for HPV-negative women in Europe is at least 5 years and may be extended up to 10 years depending on age and screening history [9,10].

In the United States, three possible screening strategies are currently recommended: screening every 3 years with cytology alone, every 5 years with HPV testing alone or every 5 years with HPV testing in combination with cytology (co-testing) in women 30–65 years. In contrast, European guidelines recommend against co-testing at any given age due to a lack of appropriate benefit [8–12].

Although it is generally accepted that HPV-based screening under age 30 is undesirable, the age to stop screening remains elusive due to insufficient empirical evidence. A recent modelling study estimated the remaining lifetime risk of cervical cancer at different exit ages and with different exit screening tests [13]. The study showed that cervical cancer in later life could be prevented with cytology screening up to age 75, but women with an HPV-negative screen result after age 55 were predicted to be at low risk of cervical cancer for the rest of their lives [13].

The most important concern is women who never or irregularly participate in screening. One option for these women is self-sampling with sample kits offered in communities or mailed to their homes. An updated meta-analysis evaluating the diagnostic accuracy of self-sampling showed that PCR-based high-risk HPV (hrHPV) assays were equally sensitive for underlying CIN2+ or CIN3+ on self-samples versus clinician-collected samples, but hrHPV assays based on signal amplification were less sensitive [14]. The efficacy analysis of different self-sampling strategies showed that offering self-sampling kits was generally more effective in reaching underscreened women than sending invitations [14].

Another important issue is the enormous number of commercial HPV assays on the market [15], which complicates choosing the best test for cervical cancer screening programmes. Only clinically validated HPV tests that demonstrate reproducible, consistently high sensitivity for CIN2+ and CIN3+ lesions and only minimal detection of clinically irrelevant transient HPV infections should be used [9,10]. Thus, the vast majority of commercially available HPV assays remain unsuitable for screening because there are no valid performance evaluations in peer-reviewed literature. As of July 2019, only 15 HPV assays fulfil international consensus guideline criteria for primary cervical cancer screening [16–18], and only five have negative predictive value longitudinal data for more than 36 months. According to European guidelines, HPV-based screening should only be performed in qualified laboratories accredited by an authorized accreditation body and in compliance with international standards, and exclusively within a population-based programme. In addition, the authorized laboratory should perform a minimum of 10 000 HPV tests annually [9,10].

Current status of implementation of HPV-based screening in Europe

To present the most recent information about the current status of primary HPV-based cervical cancer screening in Europe, the data summarized below were obtained from peer-reviewed literature, abstracts and presentations on major HPV-related conferences, personal communication with national experts and authorities involved in formulating national/regional recommendations and practical guidelines, and reviewing relevant national websites of all countries in a broader European geographical region. The eligibility criteria for a country to be included in the review was any undeniable official activity towards the implementation of primary HPV-based cervical cancer screening on national/regional level. The summary of current status of implementation of HPV-based cervical cancer screening in selected European countries and main characteristics of the screening programmes are presented in Table 1.

European countries with implemented national HPV-based screening

The Netherlands

The Netherlands is currently the most successful European country in transforming its cervical cancer screening programme from cytology-based to HPV-based screening. From January 2017, the new HPV-based screening programme covers all women age 30–60 (65 if they were HPV-positive at the last screening), who are invited and screened every 5 years until they reach age 40 and every 10 years thereafter; women age 45 and 55 are invited only if they missed screening 5 years ago or were HPV-positive at the last screening [19]. Clinical samples are taken by general practitioners (GPs), and self-sampling is offered to non-responders. For HPV-positive samples, cytology is used as a triage test (immediately and on repeat testing 6–12 months later, if necessary). There are five accredited laboratories in the country performing all HPV testing within the programme (down from 40 laboratories performing cytology testing previously) with daily throughput of at least 450 samples per laboratory site. The Netherlands issued a central national tender for laboratories, HPV test, and self-sampling devices used in the screening programme. The HPV prevalence in the first year was around 9% in clinician-collected samples (93.4% of all samples) and 7% in self-sampling (6.6% of all samples; of those, 30% were from women who had not previously participated in

Table 1
Summary of current status of implementation of HPV-based cervical cancer screening in selected European countries and main characteristics of the screening programmes

Country	Implementation phase	Screening programme organisation	Year of implementation	Age range of women screened within the programme	Screening interval	Primary test used in the screening programme	Triage test used in the screening programme
The Netherlands	Implemented	National	2017	30–60 (65 if HPV-positive at the last screening)	5 years until age 40 10 years after age 40	HPV test	Cytology
Turkey	Implemented	National	2014	30–65	5 years	HPV test	Reflex HPV16/18 genotyping and cytology
Italy	Implementation ongoing	Regional	2014–2018	30–64	5 years	HPV test	Cytology or HPV16/18 genotyping
Sweden	Implementation ongoing	Regional	2017	23–64	3 years until age 49 7 years after age 49	HPV test in women after age 30; cytology in women age 23–29	Cytology
Finland	Implementation ongoing	Regional	2016	30–60 (some municipalities 25–65)	5 years	HPV test or cytology	Cytology
Spain	Implementation ongoing	Regional	2014	25–65	3 years for cytology 5 years for HPV or co-testing	Three options in women after age 31: cytology, HPV test or co-testing; cytology in women age 25–30	Cytology or HPV test or co-testing (depending on regional recommendations)
Norway	Implementation planned	National	2019–2021	25–69	3 years for cytology 5 years for HPV	HPV test in women after age 34, cytology in women age 25–33	Cytology
Denmark	Implementation planned	National	2020	23–65	3 years for cytology 5 years for HPV	HPV test replacing cytology in at least 50% in women age 30–59; cytology in women age 23–29; HPV test in women age 60–65	Cytology
United Kingdom	Implementation planned (ongoing in Wales)	National	Wales: 2018; England, Scotland, and Northern Ireland: 2019/2020	25–65	3 years until age 50 5 years after age 50	HPV test	Cytology
Belgium	Implementation planned	National	2020/2021	25–64	5 years	HPV test in women after age 30; cytology in women age 25–29	Cytology
Germany	Implementation planned	National	2020	20–60	Yearly for cytology 3 years for co-testing	Co-testing in women after age 35; cytology in women age 20–34	Cytology in women age 20–29, co-testing in women after age 30
Malta	Implementation ongoing	National	NA	>25	3 years for cytology 5 years for VIA or HPV	HPV test in women after age 30 or cytology in women age 25–50; visual inspection with acetic acid (VIA) in women after age 50	Cytology or HPV test

NA, no data available.

screening) [20]. Due to higher sensitivity of HPV testing, the referral rate increased from 0.9% to 2.9% from the start of the new programme, but the detection rate of CIN3+ and cervical cancer requiring immediate treatment was also significantly higher [19,20].

Turkey

Turkey redesigned its cervical cancer screening programme in 2014. The programme is now based on primary HPV testing with reflex HPV16/18 genotyping and cytology triage [21,22]. Samples are taken by GPs or trained nurses from women age 30–65 invited for screening every 5 years. There are only two 'mega' HPV laboratories in the country (in Ankara and Istanbul), each performing up to 30 000 HPV tests per week, or approximately 1 million annually [21,22]. The HPV prevalence is strikingly lower than in the Netherlands: among 3.8 million women screened from 2014 to 2018, the HPV positivity rate was only around 4.29% [22]; the colposcopy referral rate was also low (1.6%), and they showed that a cytology-based programme could miss 45.9% of CIN3+ cases [21]. Since the introduction of the new screening programme, coverage has increased up to tenfold, from around 3% in 2012 to 35% in 2017 [22].

European countries with implemented regional HPV-based screening

Italy

The Italian National Prevention Plan (2014–2018) set the objective of transforming cytology-based screening to HPV-based screening, raised the starting age from 25 to 30 years, and prolonged the screening interval from 3 to 5 years. Five regions started HPV-based screening in 2015/2016, with cytology or HPV16/18 genotyping triage, using different but all clinically validated HPV tests. Data from almost 73 000 women within ten organized regional screening programmes showed an HPV positivity rate of 5.9% in women 35 or older; the cumulative referral rate from both rounds (immediate or delayed referral) was 3.6%, and 4.2 women per 1000 had CIN2+ detected [23].

Sweden

After a randomized health services study in 2012–2016 that enrolled 400 000 women, HPV-based screening was recommended by the National Board of Health and Welfare and implementation guidelines were adopted in January 2017. Sweden is currently in the implementation process and, as of May 2019, 12 of 21 regions have already implemented or partially implemented HPV-based cervical cancer screening [24]. Cytology-based screening is performed in women age 23–29, followed by HPV-based screening in women age 30–64 at 3-year intervals until age 49, and 7-year intervals thereafter.

Finland

After a recommendations update in 2016, either a cytology or HPV test with a 5-year interval and target age range 30–60 years (some municipalities also invite 25- and 65-year-old women) is used as the screening test in the Finnish programme [25]. A recent study describing 3 years of experience with regional HPV-based screening implementation including almost 48 000 women showed that the relative sensitivity of the HPV test with cytology triage compared with conventional screening was 1.64 (95% CI 1.05–2.55) for CIN2+ and 2.06 (95% CI 1.17–3.41) for CIN3+, with equal specificity [26]. Referral of all women with persistent hrHPV infection for colposcopy increased 2.3-fold; however, the detection rate of CIN2+ and CIN3+ lesions was 3.8-fold higher in the HPV-screening group versus conventional screening group [26].

Spain

Current Spanish cervical cancer screening guidelines recommend cytology screening in women age 25–30. For women over 30, three options are recommended: HPV-based screening every 5 years (preferred option), cytology screening every 3 years, or co-testing every 5 years. Considering co-testing, the Spanish Society of Epidemiology clearly stated that this option has only a transitory purpose during the implementation phase [27,28]. After age 65, screening can stop if a woman has no history of CIN or cervical cancer in the past 20 years and all previous screening tests in the past 10 years have been negative [27,28]. Unfortunately, significant heterogeneity in screening policy still exists in 17 autonomous Spanish communities. Most programmes are still opportunistic, with different levels of implementation of national guidelines [27].

European countries with national HPV-based screening in implementation phase

Norway

Norway introduced HPV-based screening in four counties in 2015 and continued with randomized implementation, which allowed an immediate comparison of short-term endpoints for both screening methods and continuous adjustments of the implementation process [29]. Currently, Norway is in a national implementation process (planned 2019–2021) with cytology-based screening of women age 25–33 every 3 years, followed by HPV-based screening in women age 34–69 at 5-year intervals.

Denmark

Consensus guidelines were issued by the Danish National Health Authority Commission in 2018. Preliminary guidelines include an option to use cytology every 3 years to screen women age 23–29 and HPV testing replacing cytology in at least 50% of all women age 30–59, whereas in women age 60–65 only HPV-based screening is envisaged. In 2014, the Central Denmark Region introduced HPV testing as a primary screening method for women age 60–64 as an 'exit test'; HPV-negative women were excluded from further screening [30]. Currently, the launch of national HPV-based screening is planned for January 2020. Regions in Central and South Denmark have conducted or are currently conducting several self-sampling pilot studies for non-attenders.

United Kingdom

Wales switched from cytology-based to HPV-based screening in 2018, whereas England, Scotland and Northern Ireland will initiate the new screening programme in 2019/2020. The revised screening programme will include women age 25–65 with 3-year recall until age 50 and 5-year recall thereafter. An increase in the screening interval to 5 or 6 years for HPV-negative women is expected in the near future. A recent large observational pilot study involving over 500 000 women showed that HPV-based screening increased the detection rate of CIN3+ and cervical cancer by approximately 40% and 30%, respectively, compared with liquid-based cytology [31].

Belgium

In July 2018, it was decided to switch to HPV-based screening to every 5 years for women age 30–64, preceded by cytology screening in women age 25–29. Reflex cytology is planned as a triage approach in the new Belgium screening programme, but this is still to be defined according to ongoing meta-analysis. The full implementation is planned for 2020/2021.

Germany

Despite European recommendations against co-testing and annual screening, the draft initiative of the German Federal Joint Committee incorporates a screening algorithm with yearly cytology for women age 20–34, followed by cytology and HPV co-testing every 3 years for women after age 35 [32]. The new programme is expected to be implemented by 2020.

Malta

Current screening recommendations in Malta include cytology every 3 years in women age 25–50, visual inspection with acetic acid every 5 years over age 50, and/or HPV testing every 5 years in women over 30 [33].

Future prospects

Due to very heterogeneous cervical cancer screening practices and inadequate implementation of preventive programmes, there are up to tenfold differences in cervical cancer age-standardized mortality rates across countries in Europe [34]. Progress towards optimal cervical cancer control faces various obstacles and a considerable amount of work still lies ahead before universal screening is available for all European women at risk of developing cervical cancer. For effective reduction of the burden of the disease, a cervical cancer screening programme must be organized (with a documented screening policy defining at least the eligible population, screening intervals and screening tests used), and population-based, with high coverage of the target population, and it should use a high-quality screening test [35]. Unfortunately, despite a European Commission directive, the rollout of population-based organized cervical cancer screening has been completed in only nine of 28 EU countries [35]. Compared to remarkable progress in colorectal cancer screening programmes in the EU in the last 10 years, which were mainly introduced directly as population-based from the beginning, converting the opportunistic approach traditionally used in cervical cancer screening practice in most of Europe to population-based screening is undoubtedly much more challenging [35]. In a country where no organized screening is available, an individual patient could benefit from an HPV test used in line with national/regional clinical guidelines. However, control of cervical cancer can be achieved only

through a population-based approach. Since population-based HPV screening is only recommended in organized screening settings [10], a well-functioning national or regional screening programme is a prerequisite for implementing HPV-based cervical cancer screening.

HPV-based cervical cancer screening is more sensitive than cytology for detecting underlying CIN2+, CIN3+ and cervical cancer, is more accurate and objective, is less variable than cytology, requires less training, shows better reproducibility, offers a possibility of self-sampling for non-attenders, and provides safe extension of screening intervals in women with a negative screening result [3,6,9,10]. In light of extensive evidence and successful implementation of HPV-based screening in some European countries and Australia, policy-makers across Europe are urged to review current cytology-based screening policies and strongly consider prompt transition to HPV-based cervical cancer screening.

Transparency Declaration

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